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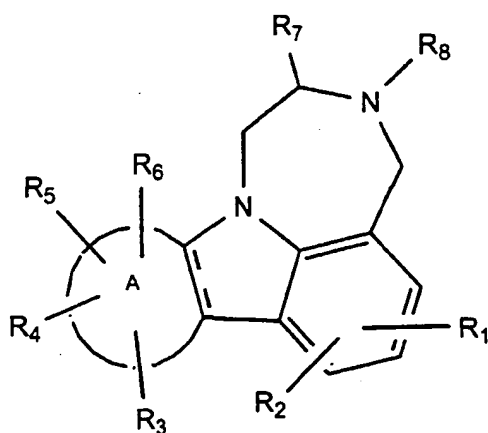
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(54) Title: CYCLOALKYL[b][1,4]DIAZEPINO[6,7,1-hi]INDOLES AND DERIVATIVES



(I)

(57) Abstract: This invention provides cycloalkyl[1,4] diazepino[6,7,1-hi] indole compounds of the formula (I); or a pharmaceutically acceptable salt thereof, as well as methods and pharmaceutical compositions utilizing them for the treatment or prevention of disorders such as obsessive-compulsive disorder, depression, anxiety, schizophrenia, migraine, sleep disorders, eating disorders, obesity, epilepsy, and spinal cord injury.

CYCLOALKYL[b][1,4]DIAZEPINO[6,7,1-hi]INDOLES AND DERIVATIVES

The present invention relates to new and known cycloalkyl[b][1,4]-diazepino[6,7,1-hi]indoles and derivatives thereof, processes for their preparation and
5 pharmaceutical compositions containing them which are serotonin 5-hydroxytryptamine 2_C (5HT_{2C}) receptor agonists useful for the treatment or prevention of disorders such as obsessive-compulsive disorder, depression, anxiety, generalized anxiety disorder, schizophrenia, panic disorder, migraine, sleep disorders, such as sleep apnea, eating disorders, such as hyperphagia, obesity, epilepsy, and spinal cord injury.

10

Background of the Invention

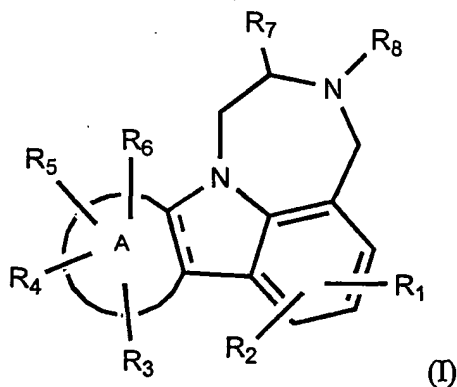
Obesity is a medical disorder characterized by an excess of body fat or adipose tissue. Comorbidities associated with obesity are Type II diabetes, cardiovascular
15 disease, hypertension, hyperlipidemia, stroke, osteoarthritis, sleep apnea, gall bladder disease, gout, some cancers, some infertility, and early mortality. As the percentage of obese individuals continues to rise both in the U.S. and abroad, obesity is expected to be a major health risk in the 21st Century. The serotonin 5-hydroxytryptamine (5-HT) receptor is a G-protein coupled receptor which is expressed in neurons in many regions
20 of the human central nervous system. [Wilkinson, L. O. and Dourish, C. T. in *Serotonin Receptor Subtypes: Basic and Clinical Aspects* (ed. Peroutka, S. J.) 147-210 (Wiley-Liss, New York, 1991).] The 5HT_{2c} receptor (formerly called the 5HT_{1C} receptor) is a prominent subtype of the serotonin receptor found in the central nervous system of both rats and humans. It is expressed widely in both cortical and subcortical regions.
25 [Julius, D. MacDermott, A. B., Axel, R. Jessell, T. M. *Science* 241:558-564 (1988).] Studies in several animal species and in humans have shown that the non-selective 5HT_{2C} receptor agonist, *meta*-chlorophenylpiperazine (MCPP) decreases food intake. [Cowen, P.J., Clifford, E. M. , Williams, C., Walsh, A. E. S., Fairburn, C. G. *Nature* 376: 557 (1995).] Tecott, *et al* have demonstrated that transgenic mice lacking the
30 5HT_{2C} receptor eat more and are heavier than Wild Type mice. [Tecott, L. H., Sun, L.

M., Akana, S. F., Strack, A. M., Lowenstein, D. H., Dallman, M. F., Jullus, D. *Nature* 374: 542-546 (1995).] Compounds of this invention are 5HT_{2C} receptor subtype selective agonists which are selective over other monoamine receptors, causes a reduction in food intake and result in a reduction in weight gain. Other therapeutic indications for 5HT_{2C} agonists are obsessive compulsive disorder, depression, panic disorder, schizophrenia, sleep disorders, eating disorders, epilepsy, and spinal cord injury.

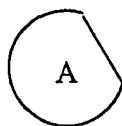
United States Patent 3,914,250 (October 21, 1975) describes 1,4-diazepino[6,5,4-jk]carbazoles as anticonvulsant agents. This invention relates to new and known cycloalky[b][1,4]diazepino[6,5,4-jk]indoles and derivatives which bind to and activate 5HT_{2C} receptors in the CNS and are useful for the treatment of CNS disorders which can benefit from modulation of the 5HT_{2C} receptor.

Description of the Invention

This invention provides a method of treatment of obsessive-compulsive disorder, depression or anxiety in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of formula (I):



wherein:



is a 6-8 membered cycloalkyl ring;

R_1 and R_2 are independently selected from hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, $-\text{CH}_2\text{-cycloalkyl}$ of 3 to 7 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of 1-6 carbon atoms, $-\text{CN}$, $-\text{NH-}$
5 $\text{SO}_2\text{-alkyl}$ of 1-6 carbon atoms, $-\text{SO}_2\text{-NH-alkyl}$ of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, aroyl and heteroaroyl;

R_3 , R_4 , R_5 and R_6 are independently selected from hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$
10 cycloalkyl, $-\text{CH}_2\text{-cycloalkyl}$ of 3 to 7 carbon atoms, $\text{C}_1\text{-C}_6$ alkoxy or $\text{C}_3\text{-C}_6$ cycloalkoxy;

R_7 is hydrogen or alkyl of 1-6 carbon atoms;

R_8 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl; and

the dashed line indicates an optional double bond;

15 or a pharmaceutically acceptable salt thereof.

This invention further provides novel compounds having formula (I) defined above.

20 In the definitions of R_1 and R_2 herein, the fluorinated alkyl and fluorinated alkoxy groups indicate the specified alkyl or alkoxy groups having any amount of fluorine substitution, including, but not limited to, groups such as $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{C}_2\text{F}_5$, $-\text{OCF}_3$, etc.

25 The compounds of formula (I) can possess one or more asymmetric centres and accordingly the compounds may exist and be isolated in a number of optically active stereoisomeric forms. While shown without respect to stereochemistry in formula (I), this invention encompasses the compounds of formula (I) in any optically active or

geometric form or mixtures thereof eg, racemates, enantiomers or diastereoisomers. Standard separation techniques may be used to isolate particular enantiomeric and diastereomeric forms. For example a racemic mixture may be converted to a mixture of optically active diastereoisomers by reaction with a single enantiomer of a 'resolving agent' (for example by diastereomeric salt formation or formation of a covalent bond).
5 The resulting mixture of optically active diastereoisomers may be separated by standard techniques (e.g crystallisation or chromatography) and individual optically active diastereoisomers then treated to remove the 'resolving agent' thereby releasing the single enantiomer of the compound of the invention. Chiral chromatography (using a
10 chiral support, eluent or ion pairing agent) may also be used to separate enantiomeric mixtures directly.

Stereospecific synthesis using optically active starting materials and/or chiral reagent catalyst and/or solvents may also be employed to prepare particular
15 diastereoisomers or even a particular enantiomer.

The term "alkyl" on a group or part of a group, e.g., alkylamino or alkoxy, includes both straight- and branched-chain saturated aliphatic hydrocarbon groups, e.g., methyl, ethyl, propyl, isopropyl and butyl. Halogen is defined as Cl, Br, F or I.
20

Examples of cycloalkyl as a group or part of a group (eg cycloalkoxy) are rings of 3-6 carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "acyl" includes alkanoyl of 2-7 carbon atoms, e.g., acetyl and
25 propanoyl.

The term "aroyl" is defined as an aryl-CO-, where aryl is defined as an aromatic system of 6-14 carbon atoms, which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms

the conjugated aromatic system. Preferred aryl groups include phenyl, naphthyl, anthryl, tetrahydronaphthyl and phenanthryl groups

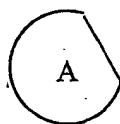
Heteroaroyl is defined as heteroaryl-CO- wherein heteroaryl includes mono- or
5 bi-cyclic rings having 5-10 ring members and 1-3 heteroatoms, the same or different, selected from O, N and S, for example thienyl, furanyl, pyrrolyl, pyridinyl or pyrimidinyl..

In the definitions used herein such as for each of R_1 and R_2 , the aroyl group is
10 preferably benzoyl. The heteroaroyl group is preferably thienoyl.

It will be understood that the dashed line in Figure I, above, indicates the optional reduction in the portion of the structure depicted.

15 Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids.

20



may be for example be six-, seven- or eight- membered, e.g., cyclohexyl, cycloheptyl or cyclooctyl.

R_1 and R_2 may each be for example independently selected from hydrogen,
25 alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of 1-6 carbon atoms and fluorinated alkoxy of 1-6 carbon atoms.

Preferably R_1 and R_2 may be each independently selected from hydrogen, alkyl of 1-6 carbon atoms and halogen.

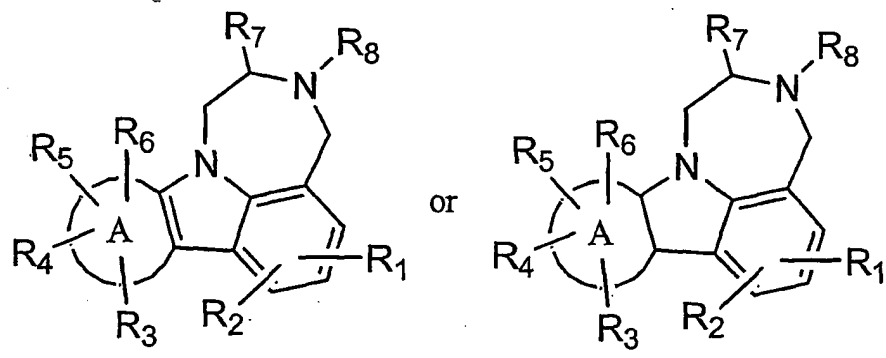
R_3 , R_4 , R_5 and R_6 may be for example each independently selected from hydrogen, C_1 - C_6 alkyl and C_1 - C_6 alkoxy.

Preferably R_1 to R_8 may be each independently hydrogen.

Preferred aroyl and heteroaroyl groups are respectively benzoyl and thienoyl.

5

A preferred group of compounds of this invention comprises compounds of formula (I) having the structure;



wherein R_1 and R_2 are each independently selected from hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, trifluoromethyl, -CN, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, and trifluoromethoxy.

A preferred group of compounds of this invention comprises those having the formula I, above, wherein R_1 , R_2 , R_8 and R_7 are each hydrogen and R_3 , R_4 , R_5 and R_6 are as defined above, or a pharmaceutically acceptable salt thereof. Another preferred group of compounds of this invention are those of formula I wherein R_1 , R_2 , R_5 , R_6 , R_8 and R_7 are each hydrogen and R_3 and R_4 are as defined above, or a pharmaceutically acceptable salt thereof.

20

Another preferred group of compounds of this invention are those of formula I wherein R_7 is hydrogen and R_1 to R_6 and R_8 are as defined above, or a pharmaceutically acceptable salt thereof. Another preferred group of compounds of this invention are

those of formula I wherein R₂, R₃ and R₇ are hydrogen and R₁, R₄ to R₆ and R₈ are as defined above, or a pharmaceutically acceptable salt thereof.

Further preferred compounds of this invention are those in which R₁-R₆ are each
 5 hydrogen. Especially preferred are compounds which are enantiomerically pure stereoisomers of compounds where R₁ is hydrogen and the indole ring is reduced or not reduced.

Specifically preferred compounds of this invention are:

- 10 (a) 1,2,3,4,8,9,10,11-Octahydro-[1,4]diazepino[6,5,4-jk]carbazole;
- (b) 1,2,3,4,7b,8,9,10,11,11a-Decahydro-[1,4]diazepino[6,7,1-jk]carbazole;
- (c) 8,8,10,10-Tetramethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]-carbazole;
- (d) 9,9-Dimethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
- 15 (e) 6-Chloro-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
- (f) 6-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
- (g) (2S)-2-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
- (h) (2R)-2-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
- (i) 6-Chloro-3-ethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,5,4-jk] carbazole;
- 20 (j) 1,2,3,4,9,10,11,12-Octahydro-8H-cyclohepta[b][1,4]diazepino[6,7,1-hi]indole;
- (k) 1,2,3,4,8,9,10,11,12,12a-Decahydro-7bH-cyclohepta[b][1,4]diazepino[6,7,1-hi]-indole;
- (l) 1,2,3,4,9,10,11,12-Octahydro-8H-cyclohepta[b][1,4]diazepino[6,7,1-hi]indole;
- (m) 1,2,3,4,8,9,10,11,12,13-Decahydrocycloocta[b][1,4]diazepino[6,7,1-hi]indole;
- 25 or a pharmaceutically acceptable salt thereof.

The 5HT_{2C} receptor agonists of this invention are useful for the treatment or prevention in mammals, preferably in humans, of disorders involving the central nervous system such as obsessive-compulsive disorder, depression, atypical depression,
 30 bipolar disorders, anxiety, generalized anxiety disorder, schizophrenia, psychoses, personality disorders, organic mental disorders, behavioral disorders associated with

dementia or age-related conditions, aggressivity, drug and alcohol addiction, social phobias, sexual dysfunction, panic disorder, migraine, sleep disorders, such as sleep apnea, eating disorders, such as hyperphagia, bulimia or anorexia nervosa, obesity, epilepsy, and premenstrual tension..

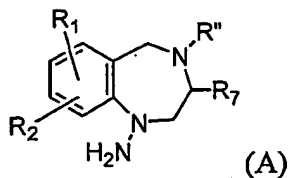
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This invention also includes methods of utilizing the compounds herein in treatments or preventative regimens for treatment of central nervous system deficiencies associated with trauma, stroke, neurodegenerative diseases or toxic or infective CNS disorders including, but not limited to, encephalitis or meningitis; or cardiovascular disorders, including thrombosis; gastrointestinal disorders such as malfunction of gastrointestinal motility; and diabetes insipidus. These methods include the improvement or inhibition of further degradation of central nervous system activity during or following the malady or trauma in question. Included in these improvements are maintenance or improvement in motor and motility skills, control, coordination and strength. This invention includes methods for treating, preventing, modulating, ameliorating or improving the condition of each of these disorders in a mammal in need thereof, the methods comprising administering a therapeutically or pharmaceutically effective amount of a compound of this invention or a pharmaceutically acceptable salt thereof.

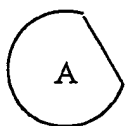
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This invention also provides processes for preparing compounds of formula (I) which processes comprise one of the following:

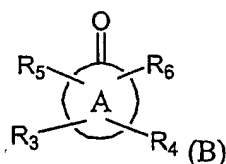
a) reacting a compound of formula (A)



25 wherein



, R₁, R₂ and R₇ are as defined above and R'' is a protecting group with a compound of formula (B)



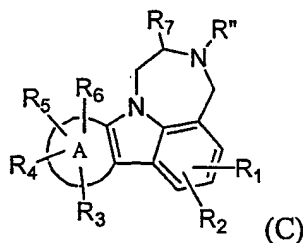
wherein R_3 , R_4 , R_5 and R_6 are as defined above followed by removal of the protecting group to give a compound of formula (I) wherein R_8 is hydrogen and the optional double bond is present;

or

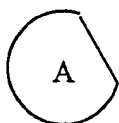
b) reducing a compound of formula (I) wherein the optional double bond is present to give a compound of formula (I) wherein the optional double bond is absent;

or

10 c) reducing a compound of formula (C)



wherein

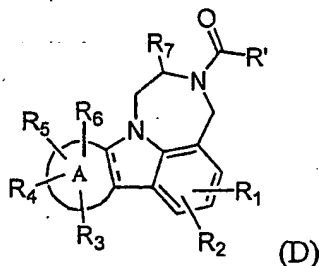


, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are as defined above and R'' is a protecting group followed by removal of the protecting group to give a compound of formula (I)

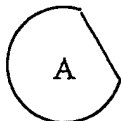
15 wherein the optional double bond is absent;

or

d) reducing a compound of formula (D)



wherein



, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are as defined above and the dashed line indicates an optional double bond;

- 5 wherein (i) R' is alkoxy; to give a compound of formula (I) wherein R_8 is methyl;

or wherein (ii) R' is C_1 - C_5 alkyl; to give a compound of formula (I) wherein R_8 is $-CH_2-(C_1-C_5 \text{ alkyl})$;

10 or

e) alkylating a compound of formula (I) wherein R_8 is hydrogen with an alkylating agent containing the group $-R_8$ wherein R_8 is C_1 - C_6 alkyl to give a compound of formula (I) wherein R_8 is C_1 - C_6 alkyl;

or

- 15 f) removing a protecting group from a compound of formula (I) in which at least one substituent carries a protecting group to give a compound of formula (I);

or

g) converting a basic compound of formula (I) to a salt thereof by reaction with a pharmaceutically acceptable acid;

20 or

h) converting a compound of formula (I) having one or more reactive substituent groups to a different compound of formula (I);

or

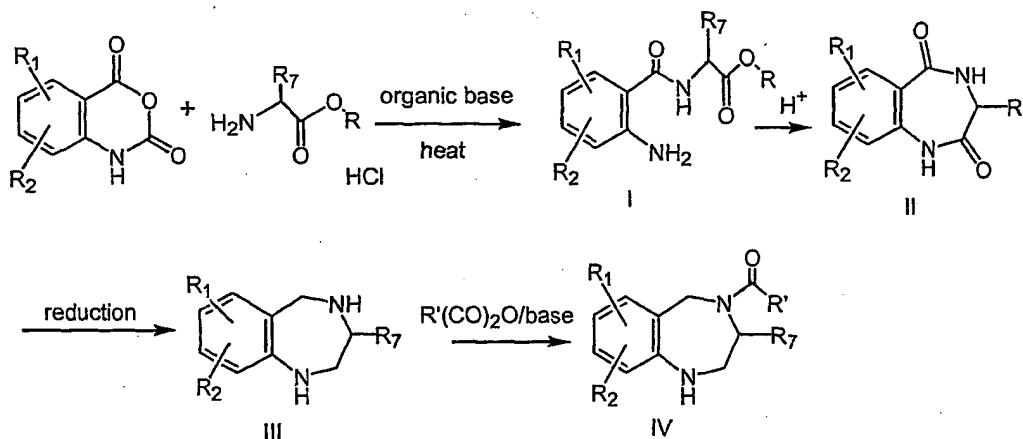
i) isolating an isomer of a compound of formula (I) from a mixture thereof.

25

If necessary, in processes above, reactive substituents or sites may be protected prior to reaction and released thereafter.

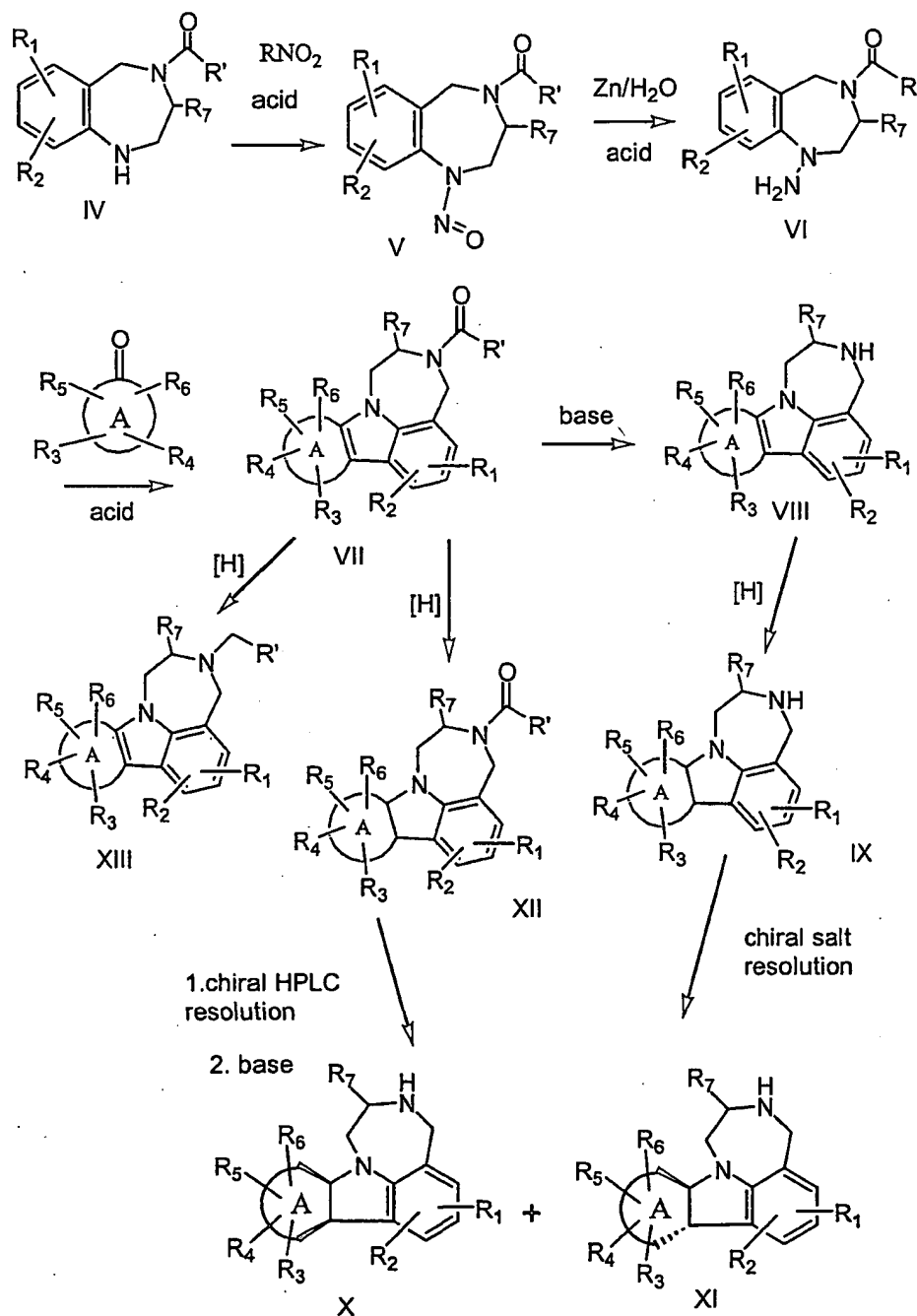
The compounds of this invention may conveniently be prepared for example according to the following schemes from commercially available starting materials or starting materials which can be prepared using literature procedures. Scheme 1 shows the preparation of a key intermediate and Scheme 2 shows the preparation of representative compounds of this invention.

Scheme 1



According to Scheme I, a substituted or unsubstituted isatoic anhydride is allowed to react with substituted or unsubstituted glycine hydrochloride or an ester of the same in an organic base such as pyridine or triethylamine, to give either open-chain intermediate I or the benzodiazepinedione II. Intermediate I can be converted to intermediate II by heating in the presence of an acid, such as acetic acid. The benzodiazepinedione II is reduced to the benzodiazepine III using a reducing agent such as lithium aluminum hydride or a borane-tetrahydrofuran complex. The secondary nitrogen atom in III is protected using a protecting group, such as an amide by reacting III with an acylating agent, such as acetic anhydride, in the presence of a base, such as triethylamine, to give an acylated benzodiazepine IV.

Scheme 2



According to Scheme 2, Intermediate IV is allowed to react with a nitrosating agent, sodium nitrite, in the presence of an acid, such as acetic acid, to give nitroso

compounds V. The nitroso compounds are reduced to hydrazines VI using a reducing agent, such as zinc powder in acetic acid and water. The hydrazines VI are allowed to react with substituted or unsubstituted cycloalkanones in acid, such as acetic acid, to give the fused indoles VII. The fused indoles VII can be treated with a base, such as NaOH, in a polar solvent, such as water or an alcohol, or with an acid, such as hydrochloric acid, to give the fused indoles VIII, which are products of this invention. In addition, fused indoles VIII can be reduced, such as by catalytic hydrogenation over a catalyst, such as palladium on charcoal, in an organic solvent, such as ethanol, in the presence of a trace of acid, such as trifluoroacetic acid, to give fused indolines IX which are products of this invention. Alternatively, fused indoles VIII can be reduced with a reducing agent, such as borane/THF or sodium cyanoborohydride in the presence of an acid, such as trifluoroacetic acid or acetic acid to give fused indolines IX which are products of this invention. Fused indolines IX are diastereoisomeric mixtures that can be resolved using chiral HPLC or chiral resolving agents to give stereo isomers X and XI and enantiomers thereof, which are products of this invention. Alternatively, fused indoles VII can be reduced, such as by catalytic hydrogenation over a catalyst, such as palladium on charcoal, in an organic solvent, such as ethanol, in the presence of a trace of an acid, such as trifluoroacetic acid, to give fused indolines XII. Fused indolines XII are diastereoisomeric mixtures which can be resolved using chiral HPLC to give separated diastereoisomers which can then be treated with an inorganic base, such as NaOH in a polar solvent, such as water or methanol at elevated temperatures, such as 50-100 °C, to remove the acyl group giving diastereoisomers X and XI which are products of this invention. Enantiomers of X and XI can also be obtained by chiral salt resolution of racemic fused indolines X and XI using a resolving agent, such as benzoyletartaric acid, in an organic solvent, such as isopropyl alcohol. Finally, fused indoles VII can be reduced with a reducing agent, such as lithium aluminum hydride or a borane-THF complex to give XIII which are compounds of this invention.

The acylation steps of this invention are understood to include reactions of the appropriate compound with any acylating agent and reaction conditions known in the art. Useful in these steps are acylating agents include acid halides and esters or anhydrides of the appropriate aliphatic carboxylic acid. Useful acid halides include
5 acetyl chloride, propionyl chloride, isobutyryl chloride, benzoyl chloride, etc. Acid anhydrides include acetic anhydride and benzoic anhydride. Similarly, alkylation steps herein are understood to include any relevant alkylating agents and conditions known in the art. These include, but are not limited to the use of alkyl halides, such as methyl iodide, or alkyl tosylates or aldehyde alkylating agents in the presence of an applicable
10 reducing agent.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric,
15 sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known pharmaceutically acceptable acids. The processes herein will be understood to include an optional additional step of forming a salt form of the products via standard addition reactions with any pharmaceutically acceptable organic or inorganic acid.

20

The ability of the compounds of this invention to act as 5HT_{2C} agonists was demonstrated in several standard pharmacological test procedures, as described below.

Test Procedures

25

5HT_{2C} Receptor Binding Test Procedure

To evaluate high affinity for the 5HT_{2C} receptor, a CHO (Chinese Hamster Ovary) cell line transfected with the cDNA expressing the human 5-hydroxy-
30 tryptamine_{2C} (h5HT_{2C}) receptor was maintained in DMEM (Dulbecco's Modified Eagle Media) supplied with fetal calf serum, glutamine, and the markers:

guaninephosphoribosyl transferase (GTP) and hypoxanthinethymidine (HT). The cells were allowed to grow to confluence in large culture dishes with intermediate changes of media and splitting. Upon reaching confluence, the cells were harvested by scraping. The harvested cells were suspended in half volume of fresh physiological phosphate buffered saline (PBS) solution and centrifuged at low speed (900 x g). This operation was repeated once more. The collected cells were then homogenized with a polytron at setting #7 for 15 sec in ten volumes of 50 mM Tris.HCl, pH 7.4 and 0.5 mM EDTA. The homogenate was centrifuged at 900 x g for 15 min to remove nuclear particles and other cell debris. The pellet was discarded and the supernatant fluid recentrifuged at 40,000 x g for 30 min. The resulting pellet was resuspended in a small volume of Tris.HCl buffer and the tissue protein content was determined in aliquots of 10-25 microliter (μ l) volumes. Bovine Serum Albumin (BSA) was used as the standard in the protein determination by the method of Lowry et al., (J. Biol. Chem., 193:265 (1951). The volume of the suspended cell membranes was adjusted with 50 mM Tris.HCl buffer containing: 0.1% ascorbic acid, 10 mM pargyline and 4 mM CaCl_2 to give a tissue protein concentration of 1-2 mg per ml of suspension. The preparation membrane suspension (many times concentrated) was aliquoted in 1ml volumes and stored at -70 C until used in subsequent binding experiments.

Binding measurements were performed in a 96 well microtiter plate format, in a total volume of 200 μ l. To each well was added: 60 μ l of incubation buffer made in 50 mM Tris.HCl buffer, pH 7.4 and containing 4 mM CaCl_2 ; 20 μ l of [125 I] DOI (S.A., 2200 Ci/mmol, NEN Life Science).

The dissociation constant, K_D of [125 I] DOI at the human serotonin 5HT_{2C} receptor was 0.4 nM by saturation binding with increasing concentrations of [125 I] DOI. The reaction was initiated by the final addition of 100.0 μ l of tissue suspension containing 50 μ g of receptor protein. Nonspecific binding is measured in the presence of 1 μ M unlabeled DOI added in 20.0 μ l volume. Test compounds were added in 20.0 ml. The mixture was incubated at room temperature for 60 min. The incubation was stopped by rapid filtration. The bound ligand-receptor complex was filtered off on a 96

well unfilter with a Packard® Filtermate 196 Harvester. The bound complex caught on the filter disk was dried in a vacuum oven heated to 60°C and the radioactivity measured by liquid scintillation with 40µl Microscint-20 scintillant in a Packard TopCount® equipped with six (6) photomultiplier detectors.

- 5 Specific binding is defined as the total radioactivity bound less the amount bound in the presence of 1 µM unlabeled DOI. Binding in the presence of varying concentrations of test drugs is expressed as percent of specific binding in the absence of drug. These results are then plotted as log % bound vs log concentration of test drug. Non linear regression analysis of data points yields both the IC50 and the Ki values of
10 test compounds with 95% confidence limits. Alternatively, a linear regression line of decline of data points is plotted, from which the IC50 value can be read off the curve and the Ki value determined by solving the following equation:

$$15 \quad K_i = \frac{IC_{50}}{1 + L/KD}$$

where L is the concentration of the radioactive ligand used and the KD is the dissociation constant of the ligand for the receptor, both expressed in nM.

- 20 The following Ki's are provided for various reference compounds:

Ki value and 95% confidence interval.

	Ritanserlin	2.0 (1.3 - 3.1) nM
	Ketanserlin	94.8 (70.7 - 127.0) nM
25	Mianserin	2.7 (1.9 - 3.8) nM
	Clozapine	23.2 (16.0 - 34.0) nM
	Methiothepin	4.6 (4.0 - 6.0) nM
	Methysergide	6.3 (4.6 - 8.6) nM
	Loxapine	33.0 (24.0 - 47.0) nM
30	mCPP	6.5 (4.8 - 9.0) nM
	DOI	6.2 (4.9 - 8.0) nM

Stimulation of [^3H] Inositol Monophosphate production by 5HT_{2C} agonists.

CHO cells transfected with the cDNA expressing the human 5-HT_{2C} receptor
5 were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with
10% fetal bovine serum and non-essential amino acids. Upon reaching confluence the
cells were harvested using PBS/EDTA and plated in 24 well plates at an initial density
of 2.5×10^5 cells per well. One (1) ml of maintenance medium containing $1 \mu\text{Ci/ml}$
myo-[^3H] inositol was added to each well. After 48 hours labeling, the cells were
10 washed once with 0.5 ml DMEM containing 25 mM HEPES and 10 mM LiCl, then
preincubated with the medium for 30 min (antagonists were included in this period if
tested). At the end of the preincubation, the medium was removed, the cells were then
incubated with test compounds (in presence of antagonists if needed) for 30 min. The
reaction was terminated by removal of the incubation solution and addition of 0.5 ml
15 ice-cold 5% PCA, followed by 15 to 30 min incubation on ice. 200 μl of 0.5 M Tes/1.5
M K₂CO₃ was added to each well to neutralize to pH 7, and plates were left on ice for
another 15 to 30 min to precipitate all salts. The liquid and solid phases were
separated by centrifugation.

20 A portion (350 μl) of the upper aqueous phase was applied to Dowex AG-1X8
(formate form, 100-200 mesh) columns. The columns were then washed stepwise with
10 ml of water and 10 ml of 25 mM ammonium formate to remove free myo-
[^3H]inositol and deacylated phosphoinositol, respectively. Finally 10 ml of 0.2 M
ammonium formate solution was applied to the columns to elute [^3H] inositol
25 monophosphate ([^3H] IP₁) directly into scintillation vials. Of this eluate, 1 ml was used
to determine radioactivity by scintillation counting.

Agonist-stimulated levels of [^3H]inositol monophosphate (IP₁) is expressed as a
percentage of the response observed with a maximally effective concentration of 5-HT

(10 μ M). A 3-parameter logistic function is used to generate estimate of EC₅₀/IC₅₀. Antagonists are tested in the presence of 10 μ M 5-HT.

The following data are provided for various reference compounds:

5	5-HT	15.1 nM	EC ₅₀
	mCPP	46.8 nM	EC ₅₀
		60%	E _{MAX} (relative to 5-HT)
	SB200646	286 nM	IC ₅₀ (10 μ M 5-HT as agonist)

10 Effects of compounds on feeding behavior in rats

Eight (8) male Sprague-Dawley rats weighing 150-180g were separated into individual cages and acclimated to a powdered diet for 2 weeks. During this period and throughout the test procedure, the food cup and the animals were weighed daily.

15 Following the acclimation period, animals were fasted for 24 hours and then injected with either vehicle or one of 4 doses of the test compound. Food intake was assessed at 2 and 24 hours following compound administration. Compounds to be evaluated were injected 1 -2 x per week until all animals had received all doses of the test compound. The order of doses were chosen using to a modified Latin Square design. Additional

20 studies may be conducted in satiated rats at the start of the dark cycle. Compounds were injected i.p, s.c. or p.o. At the end of the study effects of the test compound on food intake was evaluated using a repeated measures ANOVA. Data were collected were 2 hour food intake (g). Data were subjected to one-way ANOVA with posthoc t-tests to assess group differences. Where appropriate, ED50 values were calculated. The

25 ED50 value is the dose that produces a 50% reduction in food intake during the test period.

ResultsResults from in vitro Test Procedures

Compound	5HT _{2C} Affinity DOI/Agonist binding (K _i , nM)	5HT _{2C} % E _{max} (5HT, 100%)	Stimulation of IP3 (EC ₅₀ , nM)
Example 1	56	90	426
Example 2	92	70	207
Example 3	73		
Example 4	243		
Example 5	358		
Example 6	599		
Example 7	452		
Example 8	189		
Example 9	55% inhibition @ 1 μ M		
Example 10	38	73	500
Example 11			
Example 12	16	120	165
Example 13	65		

5

Results from in vivo 5HT_{2C} Food Intake in Rats (24 hr fast)

Compound	Route of Admin.	ED ₅₀ (mg/kg)
Example 1	ip	20.86

10 The results obtained in this standard pharmacological test procedures demonstrate that the compounds of this invention are 5HT_{2C} receptor agonists useful for the treatment of diseases involving the central nervous system such as obsessive-compulsive disorder, depression, anxiety, generalized anxiety disorder, schizophrenia, panic disorder, migraine, sleep disorders, such as sleep apnea, eating disorders, such as hyperphagia, obesity, epilepsy, and spinal cord injury.

The compounds of this invention can be formulated neat or with one or more pharmaceutical carriers or excipients for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid. This invention includes pharmaceutical compositions comprising a therapeutically or pharmaceutically effective amount of one or more compounds described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients.

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A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

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Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially

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containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can
5 also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

10 Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds of this invention can also be administered orally either in liquid or solid composition form.

15 The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered
20 transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid
25 emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a

matrix containing the active ingredient. Other occlusive devices are known in the literature.

As used herein, the terms "pharmaceutically effective amount" or
5 "therapeutically effective amount" means the total amount of each active component of
the pharmaceutical composition or method that is sufficient to show a meaningful
patient benefit, i.e., treatment, prevention or amelioration of the cause or symptoms of
the malady or condition, or an increase in rate of treatment, prevention or amelioration
of such conditions. When applied to an individual active ingredient, administered
10 alone, the term refers to that ingredient alone. When applied to a combination, the term
refers to combined amounts of the active ingredients that result in the therapeutic effect,
whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a
15 therapeutically effective amount of a compound of the present invention is
administered to a mammal having a condition to be treated. Compounds of the present
invention may be administered in accordance with the method of the invention either
alone or in combination with other therapies such as treatments employing other
pharmaceutical agents useful for treating or preventing the malady or condition in
20 question or coexisting conditions or symptoms.

The dosage requirements vary with the particular compositions employed, the
route of administration, the severity of the symptoms presented and the particular
subject being treated. Based on the results obtained in the standard pharmacological
25 test procedures, projected daily dosages of active compound would be 0.02 $\mu\text{g/kg}$ - 750
 $\mu\text{g/kg}$. Treatment will generally be initiated with small dosages less than the optimum
dose of the compound. Thereafter the dosage is increased until the optimum effect
under the circumstances is reached; precise dosages for oral, parenteral, nasal, or
intrabronchial administration will be determined by the administering physician based
30 on experience with the individual subject treated. Preferably, the pharmaceutical

composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packaged powders, vials, ampoules, pre filled syringes or sachets containing liquids.

- 5 The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

For human administration, daily dosages may be utilized from between about 0.5 µg/day to about 70,000 µg/day. More preferably, daily oral administration may include dosages from about 5mg to about 500 mg, preferably from about 10 mg to about 200 mg, more preferably from about 10 mg to about 150 mg. Intravenous administration will be at a daily dose range of from about 0.5 mg to about 75 mg, preferably from about 1 mg to about 50 mg.

- 15 The following provides the preparation of compounds representative of this invention.

Example 1

1,2,3,4,8,9,10,11-Octahydro-[1,4]diazepino[6,5,4-jk]carbazole

- 20 (Based on the procedure of D.H. Kim, US 3,914,250)

Intermediate A. 4-Acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine

- Acetic anhydride (0.60 mL) was added dropwise to a stirred suspension of 2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (950 mg, 6.4 mmol) in anhydrous ether (25 mL). After refluxing for four hours, the reaction mixture was filtered to remove a solid. Evaporation of the filtrate gave a residue which was purified by chromatography on silica gel eluting with 5% methanol in ethyl acetate. Evaporation of the product fractions gave an oil. The solid removed by filtration above contained a mixture of starting material and product by thin layer chromatography. The solid was partitioned between water and methylene chloride to remove salts and the organic portion was purified on silica gel as described above. Evaporation of the product fractions gave the

product as an oil. Both product oils were dried under oil pump vacuum and gradually solidified. The first crop of intermediate A. (322 mg) melted at 83-85 °C (lit. mp: 84-86 °C recrystallized from ether). The second crop of intermediate A (450 mg) isolated from the solid, melted at 75-79 °C.

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Anal. Calcd. for $C_{11}H_{14}N_2O$

Theory: %C, 69.44; %H, 7.42; %N, 14.73

Found: %C, 69.6; %H, 7.52; %N, 14.71

10 **Intermediate B. 3-Acetyl-1,2,3,4,8,9,10,11-octahydro-[1,4]diazepino[6,7,1-jk]-carbazole**

- Intermediate A (450 mg, 2.36 mmol) was partially dissolved in water (3.8 mL) containing conc. HCl (0.23 mL) while chilling in an ice/water bath. The ice bath was removed and a solution of $NaNO_2$ dissolved in water (0.4 mL) was added dropwise with stirring. A color change from yellow to yellow/brown resulted and an oil separated. The oil was extracted into methylene chloride, dried ($MgSO_4$), filtered and evaporated to give an oil which was dissolved in glacial acetic acid (5.4 mL). Powered zinc (1.16 g, 17.8 mmol, 7.5 eq) was added portionwise at 25-35 °C (exotherm) and the mixture was allowed to stir an additional hour after the addition of zinc was complete.
- 20 The reaction mixture was filtered into a flask containing cyclohexanone (0.27 g, 2.6 mmol, 1.12 eq) and was heated at 100°C for 1.5 h. The acetic acid was removed by evaporation under reduced pressure and the residue was purified by column chromatography on silica gel eluting with 5% methanol in methylene chloride to give 283 mg of a mixture which was further purified using chromatography on silica gel
- 25 eluting with 7% methanol in ethyl acetate to give intermediate B as a yellow solid (65 mg, 10%) mp: 124-127 °C. Lit. mp: 130-132 °C recrystallized from ether.

Anal. Calcd. For $C_{17}H_{20}N_2O$

Theory: %C, 76.08; %H, 7.51; %N, 10.44.

30 Found: %C, 75.55; %H, 7.45; %N, 10.40.

Intermediate B was treated with conc. HCl and heated under reflux for 4 h. Within 2 h. a precipitate was observed. After chilling in an ice bath, the reaction mixture was filtered to give the HCl salt of the product of Example 1 as a white solid, mp: 314-317°C. (lit. mp: 318 °C)

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Anal. Calcd. For $C_{15}H_{18}N_2 \cdot HCl \cdot 0.1 H_2O$

Theory: %C, 68.07; %H, 7.31; %N, 10.59.

Found: %C, 68.12; %H, 7.36; %N, 10.38.

10

Example 2

1,2,3,4,7b,8,9,10,11,11a-Decahydro-[1,4]diazepino[6,7,1-jk]carbazole

The product of Example 1 (506 mg, 2.23 mmol) was dissolved in anhydrous THF and treated with 1M $BH_3 \cdot THF$ (50 mL). The stirred reaction mixture was heated in an oil bath at 75-85 °C under a nitrogen atmosphere while trifluoroacetic acid was added gradually. After adding a total of 10 mL of trifluoroacetic acid and heating for 6 h, the reaction mixture was cooled to room temperature, treated with 6N HCl and stirred at room temperature overnight. The white solid which appeared was treated with conc. HCl (20 ml), warmed, swirled, and the volatiles were evaporated under reduced pressure. The white residue was suspended in methanol and evaporated two times to break up borane complexes. The residue was partitioned between ethyl acetate and aqueous NaOH. The organic phase was separated, dried ($MgSO_4$), and evaporated under reduced pressure to give a liquid residue which was purified by column chromatography on silica gel eluting with 10-20% methanol in methylene chloride. Evaporation of the pure fractions gave the product of Example 2 (80 mg) as an oil. The oil was dissolved in ether and treated with 1M HCl in ether to precipitate the dihydrochloride salt of the product of Example 2 (58 mg), mp: 265-269 °C.

Anal. Calcd for $C_{15}H_{20}N_2 \cdot 2 HCl \cdot 1 H_2O$

Calcd: %C, 56.43; %H, 7.58; %N, 8.77.

Found: %C, 56.41; %H, 7.36; %N, 8.51.

Example 3**8,8,10,10-Tetramethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-ik]carbazole****5 Intermediate C. 4-Acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepin-1-ylamine**

To a chilled reaction vessel containing 3-acetyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (15.8mmol) in H₂O (33mL) and conc. HCl (1.8mL) was added a solution of sodium nitrite (18.6mmol) in H₂O (3.1mL) dropwise. After the addition, the ice bath
10 was removed and the reaction mixture was stirred at room temperature for 20 minutes. The reaction was diluted with H₂O and extracted two times with CHCl₃. The organic layers were washed with H₂O, dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting oil was dissolved in AcOH (42mL), chilled to 0 °C, and zinc dust (138mmol) added in small portions. The ice bath was removed and the reaction
15 mixture was stirred at room temperature for 1.5 h.. Celite was added to the reaction vessel and the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to yield intermediate C.

¹H NMR (300MHz, DMSO-d₆) δ 7.4-6.7(m, 6H), 4.4(m, 2H), 3.9-3.4(m, 2H), 3.1(m, 2H), 1.9(m, 3H).

20 Crude intermediate C (7.9mmol) was dissolved in AcOH (50mL) and a solution of 3,3,5,5-tetramethylcyclohexanone (9.5mmol) in AcOH was added and heated under reflux for 18 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure to give an oil. The oil was purified by column chromatography on silica gel eluting with EtOAc to yield 3-acetyl-8,8,10,10-tetramethyl-1,2,8,9,10,11-
25 octahydro-[1,4]diazepino[6,7,1-jk]carbazole as a light, brown foam/oil (1.0mmol)

¹H NMR (300MHz, DMSO-d₆) δ 7.48(m, 1H), 6.88(m, 2H), 4.87(m, 2H), 4.12(m, 2H), 3.96(m, 2H), 2.45(m, 1H), 2.00(m, 4H), 1.52(s, 2H), 1.33(s, 6H), 1.03(s, 6H).

30 3-Acetyl-8,8,10,10-tetramethyl-1,2,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]-carbazole (1.0mmol) was dissolved in conc. HCl (4.5mL) and heated under reflux for 3 hours. The reaction was cooled to room temperature and the precipitate that formed

was collected by filtration to give the hydrochloride salt of the compound of Example 3 as a tan solid (0.144mmol).

Anal. Calc'd for $C_{19}H_{26}N_2 \cdot HCl$

5 Theory: %C, 71.56; %H, 8.53; %N, 8.78.

Found: %C, 71.61; %H, 8.74; %N, 8.62.

1H NMR (DMSO- d_6 , 400MHz) δ 9.75(s, 2H), 7.60(m, 1H), 6.99(m, 2H), 4.57(s, 2H), 4.29(m, 2H), 3.63(m, 2H), 2.48(m, 2H), 1.55(s, 2H), 1.37(s, 6H), 1.06(s, 6H).

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MS (+ESI, m/e(%)) 283(42, $[M+H]^+$).

Example 4

9,9-Dimethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole

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According to the procedure in Example 3, intermediate C (7.9mmol) in glacial acetic acid (50 mL) was allowed to react with 4,4-dimethylcyclohexanone (9.48mmol). The crude product was purified by chromatography on silica eluting with ethyl acetate to give 3-acetyl-9,9-dimethyl-1,2,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole (2.4mmol) as a tan foam/oil.

20

1H NMR (300MHz, DMSO- d_6) δ 7.23(m, 1H), 6.90(m, 2H), 4.85(m, 2H), 4.2-3.9(m, 4H), 2.66(m, 2H), 2.39(s, 2H), 2.02(d, 3H), 1.60(m, 2H), 0.98(s, 6H).

25

The tan foam/oil (2.4mmol) was treated with conc. HCl (10 mL) according to Example 3 to give the hydrochloride salt of the product of Example 4 (0.43mmol) as a yellow solid.

Anal. Calc'd for $C_{17}H_{22}N_2 \cdot HCl$

30 Theory: %C, 70.21; %H, 7.97; %N, 9.63.

Found: %C, 70.39; %H, 8.07; %N, 9.60.

¹H NMR (DMSO-d₆, 400MHz) δ 9.73(s, 1H), 7.35(dd, J=1.5Hz, 1H), 6.98(m, 2H), 4.56(s, 2H), 4.27(m, 2H), 3.67(m, 2H), 2.68(t, J=6.3Hz, 2H), 2.42(s, 2H), 1.63(t, J=6.3Hz, 2H), 0.99(s, 6H).

5 MS (EI, m/e(%)) 254(100, M⁺), 226(22), 198(100).

Example 5

6-Chloro-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-k]carbazole

10 **Intermediate D. 7-chloro-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione**

5-Chloroisatoic anhydride (50.6mmol) was stirred in H₂O (95mL) and Et₃N (75.9mmol) to give a homogenous solution. Glycine HCl (60.7mmol) was added to the reaction mixture to give a milky solution. An additional 1.5 eq. of Et₃N was added. The
15 reaction mixture was stirred at room temperature for 18 hours. After the reaction mixture was concentrated under reduced pressure, acetic acid (170mL) was added to the residue and the reaction mixture was heated under reflux for 72 hours. A precipitate formed upon cooling to room temperature. The solid was collected by filtration and washed with H₂O. The solid was dried under reduced pressure at 80° C to give 20.9
20 mmol, 41% intermediate D.

¹H NMR (300MHz, DMSO-d₆) δ 10.45(s, 1H), 8.67(m, 1H), 7.69(d, 1H), 7.57(dd, 1H), 7.12(d, 1H), 3.62(d, 2H).

25 THF (90mL) was added to intermediate D to give a heterogenous solution. The reaction flask was cooled to 0 °C in an ice/H₂O bath and 1M BH₃/THF solution (92mL) was added via a dropping funnel. After the addition was complete, the reaction mixture was stirred at room temperature for 2 hours and heated under reflux for 18 h. The reaction mixture was cooled, methanol was added and the volatiles were removed
30 under reduced pressure. This was repeated 3 times.concentrated. The final residue was

a yellow foam/oil. The crude material was crystallized in EtOAc to yield 12.5 mmol, 60% of 7-chloro-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine.

¹H NMR (300MHz, DMSO-*d*₆) δ 9.30(m, 1H), 7.34(m, 2H), 7.24(d, 1H),

5 4.11, 3.84(ABq, 2H), 3.58(m, 1H), 3.20(m, 2H), 2.91(m, 1H).

7-chloro-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (12.5mmol) was dissolved in a mixture of THF (100mL), Et₃N (19.1mmol) and acetic anhydride (12.4mmol). The reaction mixture was heated under reflux for 18 h, cooled to room temperature and
10 partitioned between H₂O and EtOAc. The aqueous phase was extracted again 2x with EtOAc and the combined organic layers were dried over MgSO₄, filtered and concentrated to a yellow, oily solid. The crude material was purified by column chromatography on silica eluting with EtOAc to yield 3-acetyl-7-chloro-1,2,3,5-tetrahydro-4*H*-[1,4]benzodiazepine (2.8mmol, 22%) as a clear oil.

15 ¹H NMR (300MHz, DMSO-*d*₆) δ 7.24(d, 1H), 7.03(m, 2H), 6.78(d, 1H), 5.80(m, 1H), 4.46(s, 1H), 4.38(s, 1H), 3.59(m, 2H), 3.09(m, 2H), 1.97(d, 3H).

To a chilled reaction vessel containing 3-acetyl-7-chloro-1,2,3,5-tetrahydro-4*H*-[1,4]benzodiazepine (2.8mmol) in H₂O (5.3mL) and concentrated HCl (321μL) was
20 added a solution of sodium nitrite (3.3mmol) in H₂O (535μL) dropwise. After the addition, the ice/H₂O bath was removed and the reaction mixture was stirred at room temperature for 20 minutes. The reaction mixture was diluted with H₂O (20mL) and extracted 2x with CHCl₃. The combined organic layers were washed H₂O, dried (MgSO₄), filtered and concentrated under reduced pressure. The oily residue was
25 dissolved in AcOH (7.5mL), chilled to 0 °C in an ice/H₂O bath, and zinc dust (24.5mmol) was added in small portions. The ice bath was removed and the reaction mixture was stirred at room temperature for 1.5 hours. Celite was added and the reaction mixture was filtered through a pad of Celite into a round-bottom flask containing cyclohexanone (3.8mmol). After heating under reflux for 3 h., the reaction
30 mixture was cooled, concentrated under reduced pressure and the residue was purified

by chromatography on silica gel eluting with ethyl acetate to give 3-acetyl-6-chloro-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole (0.770mmol, 27%).

¹H NMR (300MHz, DMSO-d₆) major rotamer δ 7.30(d, 1H), 7.03(d, 1H), 4.88(s, 2H),
5 4.18(m, 1H), 4.09(m, 1H), 4.01(m, 1H), 3.92(m, 1H), 2.67(m, 2H), 2.55(m, 2H), 2.01(s, 3H), 1.82(m, 2H), 1.71(m, 2H).

3-Acetyl-6-chloro-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole (0.770 mmol) was dissolved in conc. HCl (3.3mL) and heated under reflux for 3.5 h. The
10 reaction mixture was cooled to room temperature and the precipitate isolated by filtration, washed with a small amount of H₂O and Et₂O to yield the hydrochloride salt of the title compound (0.471mmol, 61%) as a yellow solid.

Anal. Calc'd for C₁₇H₁₉ClN₂·HCl:

15 Theory: %C, 60.62; %H, 6.10; %N, 9.42.

Found: %C, 60.62; %H, 6.15; %N, 9.29.

¹H NMR (DMSO-d₆, 400MHz) δ 9.95(s, 2H), 7.42(d, J=2.2Hz, 1H), 7.10(d, J=2.0Hz, 1H), 4.56(s, 2H), 4.26(m, 2H), 3.62(m, 2H), 2.69(m, 2H), 2.59(m, 2H), 1.83(m, 2H),
20 1.73(m, 2H).

IR (ATR, cm⁻¹) 2950, 2720, 2610, 2510, 2440, 2410, 1580, 1460, 1440, 1390, 1330, 840.

25 MS ((+)ESI, m/e(%)) 261(78, [M+H]⁺)

Example 6

6-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole

30 **Intermediate E: 4-Acetyl-7-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine**

6-Methylisatoic anhydride (10.0 g, 56 mmol) ethyl glycinate hydrochloride (9.77g, 1.25 equiv.) and anhydrous pyridine (200 mL) were combined and heated under reflux 3.5h

in a nitrogen atmosphere. The pyridine was removed by evaporation under reduced pressure to give an oil. The oil was dissolved in acetic acid (15 mL) and heated under reflux for 6 h. The volatiles were removed under reduced pressure to give a residue which was triturated methanol and filtered to recover 3.63 g of 6-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione as a yellow solid. The methanol filtrate was evaporated and acetic acid (200 mL) was added to the residue. The brown solution was heated under reflux overnight. The reaction mixture was cooled and the volume of acetic acid was reduced to half its volume under reduced pressure. Upon cooling, a solid precipitated which was collected. A second crop of 6-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (4.7 g) was obtained as a beige solid.

6-Methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (9.3 g, 49 mmol) was suspended in anhydrous THF (150 mL) under a nitrogen atmosphere. To the suspension was added 1M BH₃ in THF (200 mL, 4 equiv.) and the reaction mixture was heated under reflux for 25 h. The reaction was quenched by the careful addition of 6N HCl (200 mL) with stirring under a nitrogen atmosphere. The acidic yellow solution was extracted with ethyl acetate 2 times. Additional water and saturated NaCl solution were added to dissolve white solids. The layers were separated and the aqueous layer was chilled in an ice bath and adjusted to pH 14 with the addition of solid NaOH. The basic solution was extracted with ethyl acetate 3 times and the organic layers were combined, dried (MgSO₄), and evaporated under reduced pressure. The residue was dried under high vacuum to give 7-methylbenzodiazepine (5.76 g, 73%) as an oily solid mass.

According to the method of Intermediate A, Example 1, 2,3,4,5-tetrahydro-7-methyl-1,4-benzodiazepine (5.47 g, 34 mmol) was allowed to react with acetic anhydride (3.67 g, 34 mmol) in the presence of triethylamine (4 equiv.) in ether (500 mL) to give 7.29 g of Intermediate E as a yellow oil.

Intermediate E (7.29 g, 36 mmol) was dissolved in a mixture of water (560 mL) and conc. HCl (28 mL) and chilled in an ice bath. A solution of NaNO₂ (3.0 g, 43 mmol)

in water (125 mL) was added from a dropping funnel over 30 minutes. The ice bath was left in place the reaction mixture was allowed to gradually warm to room temperature and stir overnight. The yellow solution was extracted with CHCl_3 3 times. The organic layers were combined, dried and evaporated to give 5.28 g of crude nitroso compound. $[\text{M}+\text{H}-\text{NO}]^+$ @ m/z 204.

Intermediate F: 3-Acetyl-6-methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino-[6,7,1-jk]carbazole

10 Zinc powder (3.27 g, 3 equiv.) was sonicated in water (10 mL) for 35 min. A solution of the nitroso compound (2.64 g, 11 mmol) dissolved in acetic acid (25 mL) was added rapidly dropwise with stirring to the cold reaction mixture. The ice bath was removed and stirring was continued for 1 hr. After the reaction mixture was filtered through a sintered glass funnel to remove zinc, the yellow filtrate was evaporated under
15 reduced pressure (oil pump vacuum) to give a residue. The residue was dissolved in 1-propanol (60 mL) and p-toluenesulfonic acid hydrate (4.45 g) and cyclohexanone (6 mL, 3 equiv) were added. The reaction mixture was put into a pre-heated oil bath and heated under reflux for 1.5 h. The reaction mixture was cooled in an ice bath and neutralized (pH 6-7) with 2.5 N NaOH. The volatiles were evaporated under reduced
20 pressure to give a solid plus oil. The residue was treated with acetonitrile and intermediate F was isolated as a crystalline solid: mp 180-183 °C.

Intermediate F (340 mg, 1.2 mmol) was dissolved in conc. HCl (7 mL) and heated under reflux for 2 h. and then stirred at room temperature 2 h. The reaction mixture
25 was chilled in an ice bath and filtered to collect 230 mg of the hydrochloride salt of the compound of Example 6.

Anal. Calcd. For $\text{C}_{16}\text{H}_{20}\text{N}_2 \cdot \text{HCl} \cdot 0.25 \text{H}_2\text{O}$

Theory: %C, 68.31; %H, 7.70; %N, 9.96.

30 Found: %C, 68.70; %H, 7.67; %N, 9.94.

Example 7**(2S)-2-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-*j*k]carbazole**

Following the method of Example 5 isatoic anhydride (61.3mmol) was allowed to react
5 with L-alanine ethyl ester HCl (73.6mmol) in pyridine (200mL) to give 29.7mmol of
(3S)-3-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione as a light, brown solid.

¹H NMR (300MHz, DMSO-*d*₆) δ 10.33(s, 1H), 8.39(d, 1H), 7.72(dd, 1H), 7.48(m,
1H), 7.20(m, 1H), 7.08(d, 1H), 3.78(m, 1H), 1.21(d, 3H).

10

(3S)-3-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (29.7mmol) in THF (150
mL) and 1M BH₃/THF (130mL) gave (3S)-3-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzo-
diazepine (24.6mmol).

15 ¹H NMR (300MHz, DMSO-*d*₆) δ 9.00(s, 1H), 7.20(m, 4H), 3.94(d, 2H), 3.79(m, 1H),
3.53(m, 1H), 2.65(m, 1H), 1.07(d, 3H).

24.6mmol of the above product was allowed to react with acetic anhydride (24.0mmol)
and Et₃N (36.8mmol) in DMF (50mL) to give 1-[(3S)-3-methyl-1,2,3,5-tetrahydro-4*H*-
20 1,4-benzodiazepin-4-yl]-1-ethanone (3.3mmol) as a white solid after flash
chromatography (SiO₂) using 90:10 EtOAc/hexane.

¹H NMR (300MHz, DMSO-*d*₆) δ 7.15(m, 1H), 6.80(m, 1H), 6.52(s, 1H), 6.28(s, 2H),
4.22(m, 1H), 3.30(s, 3H, under H₂O peak), 3.01(m, 2H), 2.55(m, 2H), 1.22(m, 3H).

25

Reaction of 1-[(3S)-3-methyl-1,2,3,5-tetrahydro-4*H*-1,4-benzodiazepin-4-yl]-1-
ethanone (3.3mmol) in H₂O (6.4mL) with NaNO₂ (3.9mmol) and conc. HCl gave the
nitroso compound which was allowed to react with AcOH (8.2mL) and zinc dust
(29.1mmol) to afford the corresponding hydrazine. The hydrazine was allowed to react
30 with cyclohexanone (4.5mmol) in AcOH under reflux to give 1-[(2S)-2-methyl-
1,2,8,9,10,11-hexahydro[1,4]diazepino[6,7,1-*j*k]carbazol-3(4*H*)-yl]-1-ethanone
(1.6mmol) as a white solid.

¹H NMR (300MHz, DMSO-d₆) δ 7.21(dd, 1H), 6.85(m, 2H), 5.18(d, 1H), 4.90(m, 1H), 4.45(d, 1H), 4.24(dd, 1H), 4.11(dd, 1H), 2.66(m, 2H), 2.56(m, 2H), 1.89(s, 3H), 1.80(m, 4H), 1.15(d, 3H).

5

The above compound (1.6mmol) was heated under reflux with HCl (7.0mL) to give the hydrochloride salt of the title compound, (2S)-2-methyl-1,2,3,4,8,9,10,11-octahydro-[1,4]diazepino[6,7,1-*jk*]carbazole, as white solid (0.690mmol).

10 Anal. Calc'd for C₁₆H₂₀N₂·HCl:

Theory: %C, 69.43; %H, 7.65; %N, 10.12.

Found: %C, 69.27; %H, 7.61; %N, 9.88.

¹H NMR (DMSO-d₆, 400MHz) δ 10.1(br s, 1H), 9.6(br s, 1H), 7.36(dd, J=1.2Hz, 1H),
15 6.99(m, 2H), 4.54(s, 2H), 4.39(dd, J=2.1Hz, 1H), 3.97(m, 2H), 2.65(m, 4H), 1.86(m, 2H), 1.76(m, 2H), 1.41(d, J=6.3Hz, 3H).

IR (ATR, cm⁻¹) 2920, 2840, 2730, 2620, 2510, 2450, 1460, 1400, 1320, 740.

20 MS (EI, m/e(%)) 240(100, M⁺), 198(100), 169(86), 155(34).

Example 8

(2R)-2-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-*jk*]carbazole

25 Following the procedure of Example 5, D-alanine (73.6mmol) and isatoic anhydride (61.3mmol) were allowed to reflux in pyridine (50mL) to give (3R)-3-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (12.7mmol) as a light brown solid.

¹H NMR (300MHz, DMSO-d₆) δ 10.36(s, 1H), 8.40(d, 1H), 7.72(dd, 1H), 7.49(td,
30 1H), 7.20(td, 1H), 7.08(d, 1H), 3.80(m, 1H), 1.21(d, 3H).

(3R)-3-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione (12.7mmol) was allowed to react with 60mL 1M BH₃/THF to give (3R)-3-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine as a white foam/clear oil (8.6mmol).

- 5 ¹H NMR (300MHz, DMSO-d₆) δ 8.9(m, 1H), 7.24(m, 4H), 7.17(m, 1H), 3.94(d, 2H), 3.78(dd, 1H), 3.52(m, 1H), 2.65(m, 1H), 1.08(d, 3H).

- (3R)-3-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (8.6mmol) was allowed to react with 8.4mmol acetic anhydride and 12.9mmol Et₃N in 20mL DMF to give 2.9
10 mmol of 1-[(3R)-3-methyl-1,2,3,5-tetrahydro-4*H*-1,4-benzodiazepin-4-yl]-1-ethanone.

¹H NMR (300MHz, DMSO-d₆) major rotamer δ 6.90(m, 2H), 6.52(m, 2H), 5.69(m, 1H), 4.81, 4.18(Abq, 2H), 4.59(m, 2H), 3.39(m, 1H), 3.05(m, 1H), 1.85(s, 3H), 0.98(d, 3H).

15

- Using the same procedure as 1-[(2*S*)-2-methyl-1,2,8,9,10,11-hexahydro[1,4]diazepino-[6,7,1-*jk*]carbazol-3(4*H*)-yl]-1-ethanone with the previous compound (2.7 mmol), NaNO₂ (3.2mmol), H₂O (4mL), HCl (308μL), AcOH (7mL), zinc dust (23.6mmol) and cyclohexanone (3.7mmol) gave 0.531mmol of 1-[(2*R*)-2-methyl-1,2,8,9,10,11-hexahydro[1,4]diazepino[6,7,1-*jk*]carbazol-3(4*H*)-yl]-1-ethanone.
20

¹H NMR (300MHz, DMSO-d₆) major rotamer δ 7.20(dd, 1H), 6.84(m, 2H), 5.18, 4.46(Abq, 2H), 4.90(m, 1H), 4.10(m, 2H), 2.60(m, 4H), 1.89(s, 3H), 1.79(m, 4H), 1.15(d, 3H).

25

As described in Example 5, 1-[(2*R*)-2-methyl-1,2,8,9,10,11-hexahydro[1,4]diazepino-[6,7,1-*jk*]carbazol-3(4*H*)-yl]-1-ethanone (0.531mmol) gave the hydrochloride salt of the title compound (2*R*)-2-methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-*jk*]-carbazole as a light yellow solid (0.256mmol).

30

Anal. Calc'd for $C_{16}H_{20}N_2 \cdot HCl \cdot 0.15 H_2O$:

Theory: %C, 68.75; %H, 7.68; %N, 10.02.

Found: %C, 68.36; %H, 7.66; %N, 9.81.

- 5 1H NMR (DMSO- d_6 , 400MHz) δ 10.06(br s, 1H), 7.36(d, $J=7.6$ Hz, 1H), 7.00(m, 2H), 4.56(s, 2H), 4.39(d, $J=12.2$ Hz, 1H), 3.95(m, 2H), 2.61(m, 4H), 1.80(m, 4H); 1.41(d, $J=6.3$ Hz, 3H).

IR (ATR, cm^{-1}) 2920, 2845, 2710, 2630, 2510, 2450, 1460, 1400, 1330, 730.

- 10 MS (EI, $m/e(\%)$) 240(88, M^+), 198(100), 99(76).

Example 9

6-Chloro-3-ethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,5,4-jk]carbazole

- 15 3-Acetyl-6-chloro-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole was reduced with lithium aluminum hydride in THF by conventional methods to give an oil. The oil was dissolved in ether and treated with gaseous HCl to give the hydrochloride salt of the compound of Example 9, mp: 237-239 °C.

20 Example 10

1,2,3,4,9,10,11,12-Octahydro-8H-cyclohepta[b][1,4]diazepino[6,7,1-hi]indole

- Intermediate A (450 mg, 2.36 mmol, prepared as above) was partially dissolved in water (3.8 mL) containing conc. HCl (0.23 mL) while chilling in an ice/water bath. The
25 ice bath was removed and a solution of $NaNO_2$ dissolved in water (0.4 mL) was added dropwise with stirring. A color change from yellow to yellow/brown resulted and an oil separated. The oil was extracted into methylene chloride, dried ($MgSO_4$), filtered and evaporated to give an oil which was dissolved in glacial acetic acid (5.4 mL). Powered zinc (1.16 g, 17.8 mmol, 7.5 eq) was added portionwise at 25-35 °C
30 (exotherm) and the mixture was allowed to stir an additional hour after the addition of zinc was complete. The reaction mixture was filtered into a flask containing cycloheptanone (0.28 g, 2.6 mmol, 1.12 eq) and was heated at 100°C for 1.5 h. The

acetic acid was removed by evaporation under reduced pressure and the residue was purified by column chromatography on silica gel eluting with 3% methanol in methylene chloride to give a residue. The residue was dissolved in conc. HCl (10 mL) and heated under reflux for 5h. A precipitate formed. The reaction mixture was cooled
5 and filtered to collect a solid which was recrystallized from water to give the hydrochloride salt of the title compound as a tan solid, mp: 303-306 °C.

Anal. Calcd. For $C_{16}H_{20}N_2O \cdot HCl \cdot 0.10 H_2O$

Theory: %C, 69.98; %H, 7.67; %N, 10.10.

10 Found: %C, 68.95; %H, 7.55; %N, 10.05.

Example 11

1,2,3,4,8,9,10,11,12,12a-Decahydro-7bH-cyclohepta[b][1,4]diazepino[6,7,1-hi]-indole

15 The product of Example 10 (223 mg, 0.8mmol) was dissolved in glacial acetic acid with stirring and the solution was cooled in an ice/water bath. Solid sodium cyanoborohydride (75 mg) was added portionwise with stirring. The ice bath was removed and the reaction mixture was allowed to stir at room temperature under a
20 nitrogen atmosphere for 3 h. The volatiles were removed under reduced pressure to give a colorless oil which was partitioned between 2.5 N NaOH and ethyl acetate. The organic phase was washed with saturated NaCl solution, then water and dried ($MgSO_4$). The dried solution was filtered and the filtrate was evaporated under reduced pressure to give a pale yellow oil (206 mg).

25 The oil (196 mg) was treated with a solution of KOH (412 mg) dissolved in water (1 mL) and methanol (2 mL) and heated in an oil bath (95 °C) for 25 h. The volatiles were removed under reduced pressure to give a clear oil (120 mg). The oil was dissolved in 2-propanol and treated with an excess of ethereal HCl to give the hydrochloride salt of
30 the title compound as a yellow solid (119 mg), mp: 258-263 °C (recrystallized from 2-propanol).

Anal. Calcd for $C_{16}H_{22}N_2 \cdot HCl \cdot 0.25 H_2O$

Calcd: %C, 67.83; %H, 8.36; %N, 9.89.

Found: %C, 67.81; %H, 8.01; %N, 9.50.

5

Example 12

1,2,3,4,8,9,10,11,12,13-Decahydrocycloocta[b][1,4]diazepino[6,7,1-hi]indole

Intermediate A (5 g, prepared as above) was partially dissolved in water (50
10 mL) containing conc. HCl (3 mL) while chilling in an ice/water bath. The ice bath was
removed and a solution of $NaNO_2$ (1.8 g) dissolved in water (5 mL) was added
dropwise with stirring over 20 min. The reaction mixture was extracted into methylene
chloride, dried ($MgSO_4$), filtered and evaporated to give an oil which was dissolved in
glacial acetic acid (70 mL). Powered zinc (6.25 g) was added portionwise at 20-26°C
15 (exotherm) and the mixture was allowed to stir an additional hour after the addition of
zinc was complete. The reaction mixture was filtered into a flask containing
cyclooctanone (7 g) and was heated at 110-120°C for 3 h. The acetic acid was removed
by evaporation under reduced pressure and the residue was partitioned between 2.5 N
NaOH and ethyl acetate. The ethyl acetate was removed by evaporation under reduced
20 pressure and the residue was purified by column chromatography on silica gel eluting
with 0.3% - 0.8% methanol in methylene chloride to give 3-acetyl-
1,2,3,4,8,9,10,11,12,13-decahydrocycloocta[b][1,4]diazepino[6,7,1-hi]indole (1.51 g),
mp: 41-44°C

25 Anal. Calcd. For $C_{19}H_{24}N_2O \cdot 0.5 H_2O$

Theory: %C, 74.72; %H, 8.25; %N, 9.19

Found: %C, 74.59; %H, 8.1; %N, 8.96

3-Acetyl-1,2,3,4,8,9,10,11,12,13-decahydrocycloocta[b][1,4]diazepino[6,7,1-
30 hi]indole (1.3 g) was dissolved in methanol and diluted with 2.5N NaOH and excess
solid NaOH was added. The solution was heated at 95 °C overnight. The volatiles were

evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic phase was separated and evaporated and the residue was purified by chromatography on silica gel eluting with 3-4% methanol in methylene chloride to give a colorless oil. The oil was treated with 4 N HCl with stirring and
5 warming. The precipitate that formed was isolated by filtration, triturated with ethanol, and allowed to stand overnight. A yellow solid was isolated by filtration and dried to give the hydrochloride salt of the title compound (683 mg), mp: 316-318 °C.

Anal. Calcd. For $C_{17}H_{22}N_2 \cdot HCl$

10 Theory: %C, 70.21; %H, 7.97; %N, 9.63

Found: %C, 70.2; %H, 7.65; %N, 9.57

Example 13

1,2,3,4,7b,8,9,10,11,12,13,13a-Dodecahydrocycloocta[b][1,4]diazepino[6,7,1-hi]-

15 indole

The product of Example 12 (370 mg, 1.45 mmol) was dissolved in trifluoroacetic acid (10 mL) under a nitrogen atmosphere and cooled in an ice/water bath. 1.5 M BH_3 in THF (7 mL) was added over 4 minutes. The cooling bath was
20 removed and the reaction mixture was stirred for an additional 45 min. The reaction was quenched by the careful addition of water. Then 2.5 N NaOH was added followed by 50% aqueous NaOH until the reaction mixture remained basic. The product was extracted into methylene chloride and was purified on silica gel eluting with 3-15% methanol in methylene chloride. Evaporation of the volatiles under reduced pressure
25 gave an oil which crystallized to give the title compound as a yellow solid (238 mg), mp: 58-63 °C.

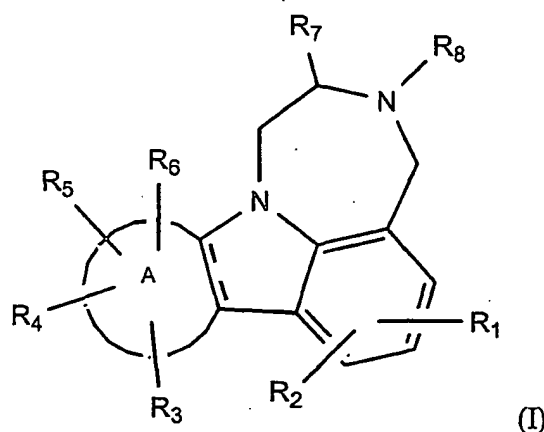
Anal. Calcd for $C_{17}H_{24}N_2 \cdot 0.4 H_2O$

Calcd: %C, 77.46; %H, 9.48; %N, 10.63.

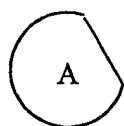
30 Found: %C, 77.48; %H, 9.29; %N, 10.54..

CLAIMS

1. A method of treatment of obsessive-compulsive disorder, obesity, eating disorders, sleeping disorders, migraine, depression, generalised anxiety disorder, schizophrenia, panic disorder, migraine, epilepsy or anxiety in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of formula (I):



wherein:



is 6-8 membered cycloalkyl ring;

- 10 R_1 and R_2 are independently selected from hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, $-\text{CH}_2\text{-cycloalkyl}$ of 3 to 7 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of 1-6 carbon atoms, $-\text{CN}$, $-\text{NH}-\text{SO}_2\text{-alkyl}$ of 1-6 carbon atoms, $-\text{SO}_2\text{-NH-alkyl}$ of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, aryl and heteroaroyl;

R_3 , R_4 , R_5 and R_6 are independently selected from hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-\text{CH}_2\text{-cycloalkyl}$ of 3 to 7 carbon atoms, $\text{C}_1\text{-C}_6$ alkoxy or $\text{C}_3\text{-C}_6$ cycloalkoxy;

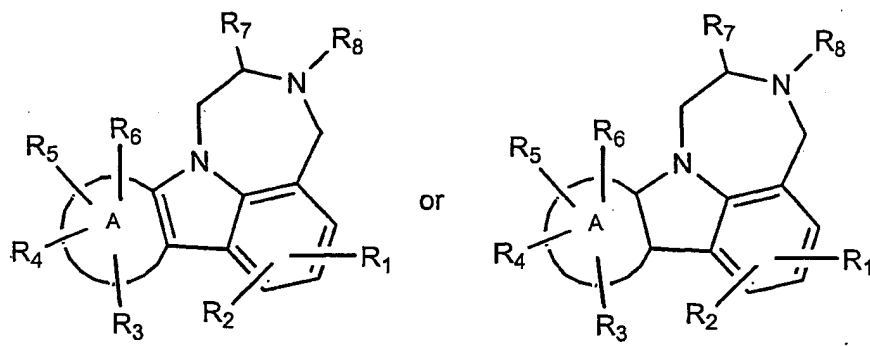
- 20 R_7 is hydrogen or alkyl of 1-6 carbon atoms;

R_8 is hydrogen or C_1 - C_6 alkyl; and

the dashed line indicates an optional double bond;

or a pharmaceutically acceptable salt thereof.

- 5 2. A method according to Claim 1 wherein the compound of formula (I) has the structure;



10 wherein R_1 and R_2 are each independently selected from hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, trifluoromethyl, -CN, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, and trifluoromethoxy.

- 15 3. A method according to Claim 1 or Claim 2 wherein R_1 and R_2 are each independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of 1-6 carbon atoms and fluorinated alkoxy of 1-6 carbon atoms.

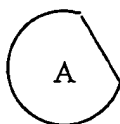
- 20 4. A method according to any one of Claims 1 to 3 wherein R_1 and R_2 are each independently selected from hydrogen, alkyl of 1-6 carbon atoms and halogen.

5. A method according to any one of Claims 1 to 4 wherein R_3 , R_4 , R_5 and R_6 are each independently selected from hydrogen, C_1 - C_6 alkyl and C_1 - C_6 alkoxy.

6. A method according to any one of Claims 1 to 5 wherein R_1 to R_8 , are each independently selected from hydrogen and C_1 - C_6 alkyl.

7. A method according to any one of Claims 1 to 6 wherein R_1 to R_8 are each independently hydrogen.

8. A method according to any one of Claims 1 to 7 wherein



is selected from cyclohexyl, cycloheptyl and cyclooctyl.

10

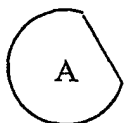
9. A method according to Claim 1 wherein the compound of formula (I) is one of the following:

- (a) 1,2,3,4,8,9,10,11-Octahydro-[1,4]diazepino[6,5,4-jk]carbazole;
 - 15 (b) 1,2,3,4,7b,8,9,10,11,11a-Decahydro-[1,4]diazepino[6,7,1-jk]carbazole;
 - (c) 8,8,10,10-Tetramethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (d) 9,9,Dimethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (e) 6-Chloro-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - 20 (f) 6-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (g) (2S)-2-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (h) (2R)-2-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (i) 6-Chloro-3-ethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,5,4-jk]carbazole;
 - (j) 1,2,3,4,9,10,11,12-Octahydro-8H-cyclohepta[b][1,4]diazepino[6,7,1-hi]indole;
 - 25 (k) 1,2,3,4,8,9,10,11,12,12a-Decahydro-7bH-cyclohepta[b][1,4]diazepino[6,7,1-hi]-indole;
 - (l) 1,2,3,4,9,10,11,12-Octahydro-8H-cyclohepta[b][1,4]diazepino[6,7,1-hi]indole;
 - (m) 1,2,3,4,8,9,10,11,12,13-Decahydrocycloocta[b][1,4]diazepino[6,7,1-hi]indole;
- or a pharmaceutically acceptable salt thereof.

10. Use of a compound of formula (I) as shown and defined in any one of Claims 1 to 9 for the preparation of a medicament for the treatment of obsessive-compulsive disorder, depression or anxiety in a mammal.

5

11. A compound of formula (I) as shown and defined in any one of Claims 1-8 with the proviso that when;



is cyclohexyl; R_1 is selected from 6-hydrogen, 6-halogen and 6- C_1-C_6 alkyl and the optional double bond is present, then at least one of R_2-R_7 is other than hydrogen;
or a pharmaceutically acceptable salt thereof.

12. A compound of formula (I) as defined in Claim 11 which is one of the following:

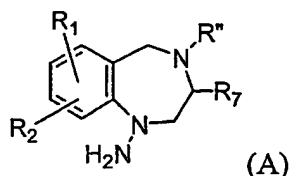
- 15 (a) 1,2,3,4,7b,8,9,10,11,11a-Decahydro-[1,4]diazepino[6,7,1-jk]carbazole;
 - (b) 8,8,10,10-Tetramethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (c) 9,9-Dimethyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (d) 6-Chloro-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - 20 (e) 6-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (f) (2S)-2-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (g) (2R)-2-Methyl-1,2,3,4,8,9,10,11-octahydro[1,4]diazepino[6,7,1-jk]carbazole;
 - (h) 1,2,3,4,9,10,11,12-Octahydro-8H-cyclohepta[b][1,4]diazepino[6,7,1-hi]indole;
 - (i) 1,2,3,4,8,9,10,11,12,12a-Decahydro-7bH-cyclohepta[b][1,4]diazepino[6,7,1-hi]-
25 indole;
 - (j) 1,2,3,4,9,10,11,12-Octahydro-8H-cyclohepta[b][1,4]diazepino[6,7,1-hi]indole;
 - (k) 1,2,3,4,8,9,10,11,12,13-Decahydrocycloocta[b][1,4]diazepino[6,7,1-hi]indole;
- or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound according to Claim 11 or Claim 12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

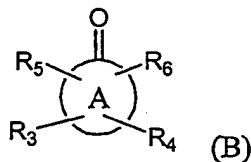
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14. A process of preparing a compound of formula (I) as defined in Claim 11 which comprises one of the following:

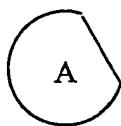
a) reacting a compound of formula (A)



10 wherein R_1 , R_2 and R_7 are as defined in claim 11 and R'' is a protecting group with a compound of formula (B)



wherein



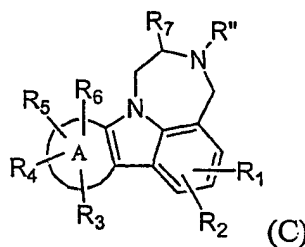
15 , R_3 , R_4 , R_5 and R_6 are as defined in claim 11 followed by removal of the protecting group to give a compound of formula (I) wherein R_8 is hydrogen and the optional double bond is present;

or

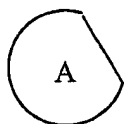
b) reducing a compound of formula (I) wherein the optional double bond is present to give a compound of formula (I) wherein the optional double bond is absent;

20 or

c) reducing a compound of formula (C)



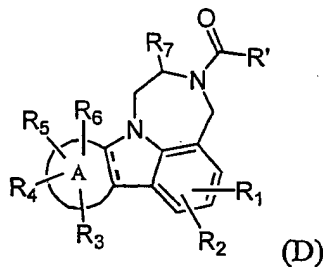
wherein



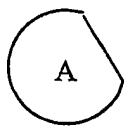
, R₁, R₂, R₃, R₄, R₅, R₆, and R₇ are as defined in claim 1 and R'' is a
 5 protecting group followed by removal of the protecting group to give a compound of
 formula (I) wherein the optional double bond is absent;

or

d) reducing a compound of formula (D)



10 wherein



, R₁, R₂, R₃, R₄, R₅, R₆, and R₇ are as defined in claim 11 and the dashed line
 indicates an optional double bond;

wherein (i) R' is alkoxy; to give a compound of formula (I) wherein R₈ is
 methyl;

15 or wherein (ii) R' is C₁-C₅ alkyl; to give a compound of formula (I) wherein R₈ is
 -CH₂-(C₁-C₅ alkyl);

or

- e) alkylating a compound of formula (I) wherein R_8 is hydrogen with an alkylating agent containing the group $-R_8$ wherein R_8 is C_1-C_6 alkyl to give a compound of formula (I) wherein R_8 is C_1-C_6 alkyl;
- or
- 5 f) removing a protecting group from a compound of formula (I) in which at least one substituent carries a protecting group to give a compound of formula (I);
- or
- g) converting a basic compound of formula (I) to a salt thereof by reaction with a pharmaceutically acceptable acid;
- 10 or
- h) converting a compound of formula (I) having one or more reactive substituent groups to a different compound of formula (I);
- or
- i) isolating an isomer of a compound of formula (I) from a mixture thereof.

15

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

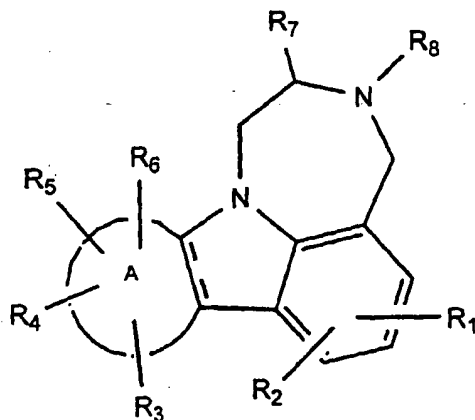
Published:

- with international search report

(88) Date of publication of the international search report:
24 October 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CYCLOALKYL[b][1,4]DIAZEPINO[6,7,1-hi]INDOLES AND DERIVATIVES



(I)

(57) Abstract: This invention provides cycloalkyl[1,4] diazepino[6,7,1-hi] indole compounds of the formula (I): or a pharmaceutically acceptable salt thereof, as well as methods and pharmaceutical compositions utilizing them for the treatment or prevention of disorders such as obsessive-compulsive disorder, depression, anxiety, schizophrenia, migraine, sleep disorders, eating disorders, obesity, epilepsy, and spinal cord injury.

WO 02/036596 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/46084

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/06 A61K31/5517 A61P25/00 //(C07D487/06,243:00,
209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 914 250 A (KIM DONG H) 21 October 1975 (1975-10-21) cited in the application claim 1; example XIV	1
X	HÄRTER, H.P. ET AL.: "Schmidt-Reaktion an Tetrahydro-chinolon-Derivaten" CHIMIA, vol. 30, no. 2, 1976, pages 50-52, XP008006029 AARAU, CH ISSN: 0009-4293 compound XVIII	12

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

17 July 2002

Date of mailing of the international search report

30/07/2002

Name and mailing address of the ISA

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Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/46084

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1 - 8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/46084

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3914250	A	21-10-1975	NONE

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